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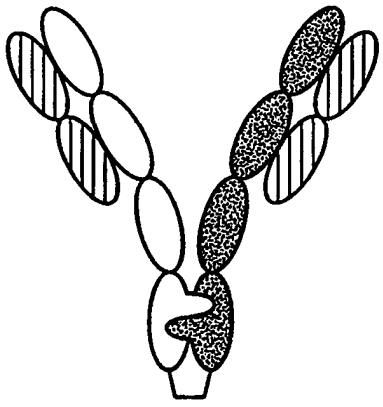
(54) Title: A METHOD FOR MAKING MULTISPECIFIC ANTIBODIES HAVING HETEROMULTIMERIC AND COMMON COMPONENTS

(57) Abstract

The invention relates to a method of preparing heteromultimeric polypeptides such as bispecific antibodies, bispecific immunoadhesins and antibody–immunoadhesin chimeras. The invention also relates to the heteromultimers prepared using the method. Generally, the method provides a multispecific antibody having a common light chain associated with each heteromeric polypeptide having an antibody binding domain. Additionally the method further involves introducing into the multispecific antibody a specific and complementary interaction at the interface of a first polypeptide and the interface of a second polypeptide, so as to promote heteromultimer formation and hinder homomultimer formation; and/or a free thiol–containing residue at the interface of a first polypeptide and a corresponding free thiol–containing residue in the interface of a second polypeptide, such that a non–naturally occurring disulfide bond is formed between the first and second polypeptide. The method allows for the enhanced formation of the desired heteromultimer relative to undesired heteromultimers and homomultimers.



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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 98/08762

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/13 C07K16/46 C12N5/10 //C07K16/28,C07K16/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VAUGHAN ET AL: "HUMAN ANTIBODIES WITH SUB-NANOMOLAR AFFINITIES ISOLATED FROM A LARGE NON-IMMUNIZED PHAGE DISPLAY LIBRARY" NATURE BIOTECHNOLOGY, vol. 14, 1996, pages 309-314, XP002084763 cited in the application	1-27
A	see the whole document	30-33

X	WO 92 10209 A (WISTAR INST) 25 June 1992	28,29
Y	see page 4, line 15 - page 5, line 9	1-27
A	see page 13, line 3 - line 18	30-33

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 November 1998	02/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sitch, W

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 98/08762

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	ZHU ET AL: "REMODELLING DOMAIN INTERFACES TO ENHANCE HETERODIMER FORMATION" PROTEIN SCIENCE, vol. 6, no. 4, April 1997, pages 781-788, XP002084764	28,29
Y	see page 781	1-27
A	see abstract	30-33
A	WELLS ET AL: "IN VIVO FORMATION AND STABILITY OF ENGINEERED DISULFIDE BONDS IN SUBTILISIN" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 261, no. 14, 15 May 1986, pages 6564-6570, XP002084765 see page 6564 see abstract see page 6566, paragraph 2 - paragraph 3	28
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A	see page 617 see abstract	30-33
Y	WO 96 27011 A (GENENTECH INC) 6 September 1996	1,2, 4-14, 16-23, 25-27
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
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